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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,798	11/12/2003	Carlo Croce	3589.1008-002	8331

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,798	CROCE ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17,52,75-97,101,102,104 and 105* is/are pending in the application.

4a) Of the above claim(s) *16,17,75-88,95 and 96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52, 89-94, 97, 101-102 and 104-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/13/08 has been entered.

Claims 16-17, 52, 75-97, 101-102 and 104-105 are pending in the present application.

Previously, Applicant's election with traverse of Group XI, **drawn to a method of treating an miR15 mediated cancer in a subject in need of such treatment using autologous cells transfected with a nucleic acid comprising sequence encoding an effective amount of an miR15 gene product**, in the reply filed on 10/6/06 is acknowledged. **Applicants also elected previously the following species: (a) prostate cancer cells as the species of transfected cells; (b) cytomegalovirus promoter as the species of promoter; and (c) an adeno-associated virus vector as the species of recombinant viral vector**.

Accordingly, claims 16-17, 75-88 and 95-96 were withdrawn previously from further consideration because they are directed to non-elected species.

Therefore, amended claims 52, 89-94, 97, 101-102 and 104-105 are examined on the merits herein **with the previously elected species**.

Priority

The present application claims benefit of the provisional application 60/425, 864, filed on 11/13/2002 and the provisional application 60/469,464, filed on 05/09/2003.

Upon review of the specifications of the above provisional applications and comparison with the specification of the present application, it is determined that examined claims 52, 89-94, 97, 101-102 and 104-105 are only entitled **at best to the effective filing date of 05/09/2003** because the provisional application 60/425,864 does not have a written support for any gene therapy concept, particularly for an ex vivo gene therapy approach, for treating any cancer including a prostate cancer tumor in a subject using transfected autologous cell containing a nucleotide sequence encoding a miR15 gene product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 52, 89-94, 97, 101-102 and 104-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

1. The breadth of the claims

The instant claims are directed to a method of treating a prostate cancer tumor in any subject comprising the step of administering to the subject any cell from any tissue source (transfected prostate cancer cells as the elected cell species) as long as it has been isolated from the subject and transfected with any nucleic acid (including the elected recombinant adeno-associated virus vector containing the elected cytomegalovirus promoter) comprising a nucleotide sequence encoding any miR15 gene product (not necessarily limited to a miR15 gene product whose gene is located at 13q14 chromosome in humans), wherein the cell is administered to the subject by direct injection into the prostate cancer tumor.

2. The state of the prior art and the unpredictability of the prior art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the instant application (11/13/2002), gene therapy was and continues to be immature and unpredictable, particularly for attaining any therapeutic effects. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression, immune

manipulation, is needed to make **gene therapy a reality**. Dang et al. also pointed out several factors limiting an effective human gene therapy, including, sub-optimal vectors, the lack of a stable *in vivo* gene expression, and most importantly **the lack of an efficient gene delivery to targeted cells or tissues** (last paragraph, page 474). Romano et al. (Stem Cells 18:19-39, 2000) state "The potential therapeutic applications of gene transfer technology are enormous. However, **the effectiveness of gene therapy programs is still questioned**", and "[d]espite the latest significant achievements reported in vector design, **it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame**" (see abstract, col. 2). Even in 2005, Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005) still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph).

Additionally, at about the effective filing date of the present application (05/09/2003), little was known about the function of microRNAs, including miR15, let alone for using these microRNA in the form of *ex vivo* gene therapy to attain a desired therapeutic effect such as treating or inhibiting proliferation of a prostate cancer tumor in a subject. Lagos-Quintana et al. (Science 294 :853-858, 2001; IDS) state "**The**

challenge for the future is to define the function and the potential targets of these novel miRNAs by using bioinformatics as well as genetics and to establish a complete catalog of time-and tissue-specific distribution of the already identified and yet to be uncovered miRNAs" (page 857, top of col. 2). Moreover, many years after the effective filing date of the present application the tumor suppressing role of the miR15 gene product, whose human gene is located at 13q14, in prostate cancer is still yet established as evidenced by the teachings of Cho (Molecular Cancer 6:1-7, 2007; see Table 1 and page 2, col. 1, last paragraph continues to first paragraph of col. 2) and Xia et al. (Int. J. Cancer 123:372-379, 2008). Even in 2008, with respect to the role of miR-15a Xia et al still stated "**So far, the tumor-suppressor role of this cluster has only been manifested in various leukaemia but not in cancers that originate form other tissues**" (page 377, col. 2, lines 1-3).

3. The amount of direction or guidance provided

Apart from disclosing that the miR15 gene is located at 13q14 within a 30-kb region of loss in human chronic lymphocytic leukemia (CLL) and prostate cancer, and 5 out of 6 analyzed prostate cancer cell lines showed a significant reduction in miR15 expression when compared with their normal tissue counterparts, the instant specification fails to provide sufficient guidance, including any relevant example, for a skilled artisan on how to attain any therapeutic effect (for this instance at least inhibition of prostate cancer cell proliferation and/or metastasis in a patient) by direct injection into the prostate cancer tumor any autologous cells, including autologous prostate cancer cells (elected species), as long as they are transfected with a recombinant adeno-

associated virus vector (elected species) expressing an effective amount of any miR15 gene product. **Firstly, there is no evidence of record or in the prior art at the effective filing date of the present application indicating that 13q14 deletions commonly observed in prostate cancers in fact contain the miR15 gene; and/or a decrease or suppression of the miR15 gene expression in prostate cancer autopsy samples or prostate cancer cell lines is correlated with the minimal 13q14 deletion containing the miR15 gene**. It should be noted that the observed down-regulation miR15 gene product in 5 out of 6 prostate cancer cell lines *in vitro* could be caused by factors that have nothing to do with a deletion or loss of a region containing the miR15 gene at 13q14 chromosome in human prostate cancers. More importantly, there is no factual evidence indicating that the tumorigenecity of any prostate cancer cells in either *in vitro* or *in vivo* is inversely proportional to the expression of a miR15 gene product whose gene is located at human 13q14 chromosome, let alone for any miR15 gene product (e.g., a similar miR15 gene on human chromosome 3q25-26.1 whose gene expression was detected and expressed in CLL samples with known large homozygous deletions at 13q14; see at least example 4 of the instant specification). The examiner further notes that with respect to prostate cancer cells, examples 6 and 11 of the instant specification are prophetic. Once again, please also note that many years after the effective filing date of the present application (5/9/2003) the tumor suppressing role of the miR15 gene product, whose human gene is located at 13q14, in prostate cancer is still yet established as evidenced by the teachings of Cho (Molecular Cancer 6:1-7, 2007) and Xia et al. (Int. J. Cancer 123:372-

379, 2008). Even in 2008, with respect to the role of miR-15a Xia et al still stated "**So far, the tumor-suppressor role of this cluster has only been manifested in various leukaemia but not in cancers that originate form other tissues**" (page 377, col. 2, lines 1-3). **Secondly, the miR15 gene product is an intracellular product.** Then how does an effective amount of the miR15 gene product expressed in implanted, genetically modified cells or prostate cancer cells exert their effect on other cancer cells in the patient that are not genetically modified to attain any desired therapeutic effect? There is no evidence of record suggesting or indicating that any recombinant miR15 gene product is diffused from prostate cells or cells transfected *ex vivo*, and it is being transported into other non-transfected prostate cancer cells in the patient at an effective concentration to yield a desired therapeutic effect. **Thirdly, available recombinant adeno-associated viral vectors at the effective filing date of the present application are replication defective. Then, how can the implanted autologous genetically modified prostate cancer cells effectively deliver an effective amount of miR15 gene product to other prostate cancer cells present in the patient to yield a desired therapeutic effect.**

Accordingly, in light of the state and the unpredictability of the gene therapy art, particularly little was known on the function of miR15 gene product in prostate cancer cells as discussed above, coupled with the lack of sufficient guidance provided by the present disclosure regarding to the aforementioned issues, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Response to Amendment

Applicant's arguments related in part to the above rejection in the Amendment filed on 6/13/08 (pages 6-10) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the instant specification provided substantial guidance to enable one skilled in the art to practice the method as claimed in independent claim 52, for example the disclosure of miR15 gene product, transfection of cells with nucleic acids encoding miR15 gene products, a variety of recombinant plasmid and viral vectors, treating a prostate cancer tumor by direct injection of cells obtained from the subject into the prostate cancer tumor. With respect to the issue of how recombinant adeno-associated viral vectors which are replication defective can yield a therapeutic effect, Applicants cited the Flotte et al reference (Exhibit A) and the Kessler et al reference (Exhibit B) showing that AAV vectors are suitable vectors for therapy and induce stable expression of nucleic acids in cells. With respect to the issue of evidence indicating or suggesting diffusion of microRNAs from cells, Applicants cited the post-filing art of Valadi et al (Nat. Cell Biol. 9:654-659, 2007; Exhibit C) to show that microRNAs, including miR15, are transferred between animal cells *in vivo* by exoxomes which are vesicles of endocytic origin that are released by many cells, including tumor cells.

Firstly, the description on how to treat a prostate cancer in a subject as claimed in independent claim 52 by itself is not sufficient or necessary that the claimed method is enabled. Please refer to the detailed analysis of the Wands factors set forth in the

above rejection on why the presently claimed invention is not enabled, particularly even in 2008, with respect to the role of miR-15a Xia et al still stated "**So far, the tumor-suppressor role of this cluster has only been manifested in various leukaemia but not in cancers that originate form other tissues**" (page 377, col. 2, lines 1-3).

Secondly, the issue is not whether recombinant replication defective AAVs can induce stable expression of nucleic acids in transfected cells. Rather, the issue is how implanted cells, including autologous prostate cancer cells, transfected with a recombinant AAV encoding a miR15 gene product, can mediate the transfer of miR15 gene product which is an intracellular gene product in ex vivo transfected cells to non-genetically modified prostate cancer cells present in the subject in an effective amount to yield any desired therapeutic effect, assuming that miR15 gene product even has a tumor suppressing activity in prostate cancer cells.

Thirdly, it should be noted that **the post-filing article of Valadi et al is about 4 years after the effective filing date of the present application (05/09/2003)**. At the effective filing date of the present application, exosome-mediated transfer of mRNAs and microRNAs between mast cells as described by Valadi et al was not even recognized or appreciated by a skilled artisan in the art. Moreover, **the exosomal shuttle RNA taught by Valadi et al is between mouse and human mast cells**, and that a similar observation is not necessarily be extended to the same extent to other cells having the capacity to release exosomes, let alone for any types of cells as broadly encompassed by certain broad claims. It should also be noted that Valadi et al stated "Moreover, **if exosomes interact with recipient cell through specific receptor-**

ligand interactions, this venue of communication could be expected to be cell type specific" (page 655, col. 2, top of last paragraph); and "**The functions of exosomes are not completely understood**, although it has been shown that exosomes can participate in the signaling events contributing to antigen presentation to T cells[4] and the development of tolerance[9]." (page 654, col. 1, middle of last paragraph). Additionally, just for the sake of argument the simple detection of microRNAs in microsomes is not necessarily an indicative that an effective amount of microRNAs is present to yield a desired therapeutic effect contemplated by Applicants for the presently claimed invention. Furthermore, it is highly unlikely that the exosome-mediated transfer of mRNAs and microRNAs is **universal for genetic exchange between all types of cells**, and the mechanism of **genetic exchange is highly effective**; because if this is true then why **the lack of an efficient gene delivery to targeted cells or tissues was and still a challenge for any gene therapy method as evidenced at least by the teachings of Dang et al, Romano et al and Verma et al.?**

Accordingly, amended claims 52, 89-94, 97, 101-102 and 104-105 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633